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Failure of dopexamine to maintain haemodynamic improvement in patients with chronic heart failure

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SUMMARY Ten patients with chronic heart failure were given a continuous infusion of dopexamine after an initial stage of dose titration. On the dose selected the cardiac index initially rose by 56%, as a result of an increase in both heart rate and stroke volume index. Systemic vascular resistance fell by 34% and the mean arterial pressure did not change. Within 18 hours of the start of the continuous infusion, however, all the variables except heart rate had returned to preinfusion values. Nine of the 10 patients were withdrawn from the 48 hour study, six because of haemodynamic deterioration and two because of side effects.

If the premature loss of therapeutic effect reflects an intrinsic property of this agent, dopexamine may be of limited clinical value.

Although dopamine may be of value in the management of chronic heart failure,[1] vasoconstriction, which results from α adrenoceptor stimulation, has limited its use.[2] Dopexamine is a new analogue of dopamine and like the parent compound it must be given intravenously. Although it is as potent as dopamine in increasing renal blood flow, the two agents have different systemic effects.[3] Because dopexamine is a potent β_2 adrenoceptor agonist with no action on α adrenoceptors it produces systemic vasodilatation.[4] And although it does not have appreciable β_1 adrenoceptor activity there is increasing evidence that dopexamine does have inotropic properties,[5] perhaps through an action on myocardial β_2 receptors.[6]

Inotropes and vasodilators are used to treat resistant heart failure and both clinical and physiological evidence support their use in combination.[7] Because dopexamine is a vasodilator with inotropic properties it may have a role in the management of such patients.

The acute haemodynamic response to dopexamine in chronic heart failure has previously been described.[8,9] Intravenous administration reduces the systemic vascular resistance and increases cardiac output; mean arterial pressure does not change. Furthermore, this occurs without a significant change in myocardial oxygen consumption or metabolic function.[8]

These studies, however, described only the immediate response to a range of dopexamine doses, with each individual dose being administered for 10 or 15 minutes. For dopexamine to be of clinical value a sustained haemodynamic response is required and the present study was designed to examine the response to continuous infusion.

Patients and methods

PATIENTS

We studied 10 patients with chronic heart failure (seven men and three women aged 51 to 69 years (mean of 60)). All were breathless at rest or on minimal effort (New York Heart Association class III or IV), and their symptoms had become worse one week to six months before admission. The cause of heart failure was ischaemic in seven patients and a dilated cardiomyopathy in three. Two patients were diabetic, one treated with an oral hypoglycaemic agent and the other insulin. One patient was in atrial fibrillation.

All were taking a loop diuretic. This was frusemide (80–1000 mg daily, mean of 350 mg) in nine and bumetanide (10 mg daily) in one. Four patients were taking digoxin and three were already taking oral vasodilators (captopril, enalapril, and flosequinan).

Before admission breathlessness had worsened in all patients, but they were judged to be clinically and haemodynamically stable before entry into the study.

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In each case their bodyweight and medication were unchanged for at least 48 hours before the start of the study. Informed consent was obtained from all patients and the protocol was approved by the hospital ethics committee.

METHODS

A balloon-tipped thermodilution catheter (Mansfield Scientific Inc) was inserted via a subclavian vein and positioned in the pulmonary artery. Pressures were measured by a fluid filled system with the patient supine and the breath held in expiration. Cardiac output was measured by thermodilution with a cardiac output computer (American Edwards Laboratory Model 9520A). The mean of three separate readings was taken. Heart rate and rhythm were monitored continuously throughout the study and arterial blood pressure was measured by a sphygmomanometer and standard adult cuff.

Heart rate, blood pressure, cardiac output (CO), and pulmonary artery pressure (PAP) were recorded in all patients. A consistent pulmonary capillary wedge pressure could not be measured in two patients and so diastolic pulmonary artery pressure, rather than wedge pressure, was used as a measure of left ventricular end diastolic pressure in these patients. This is why we used a modified formula for the calculation of pulmonary vascular resistance (PVR) with diastolic pulmonary artery pressure being used instead of pulmonary capillary wedge pressure. The formula was as follows:

$$PVR = \frac{(\text{Mean PAP}-\text{diastolic PAP})}{CO} \times 80 \text{ dyn.s.cm}^{-5}$$

Because right atrial pressure was only recorded during catheter insertion systemic vascular resistance (SVR) was calculated as follows:

$$SVR = \frac{\text{mean arterial pressure}}{CO} \times 80 \text{ dyn.s.cm}^{-5}$$

Cardiac index, stroke volume index, mean arterial pressure, and mean pulmonary artery pressure were calculated according to standard formulas.

DRUG ADMINISTRATION

Each patient was given a range of dopexamine doses and the haemodynamic response to each was assessed (stage I). The dose that produced the best haemodynamic improvement was then continued for a further 48 hours (stage II). Throughout the period of study patients continued on their regular medication.

STAGE I

After two sets of baseline readings had been taken at 15 minute intervals dopexamine (diluted in 500 ml of 5% dextrose) was infused at an initial rate of 1 μg/kg/min. The dose was subsequently increased to 2, 4, and 6 μg/kg/min, with each dose being maintained for 15 minutes. Haemodynamic variables were measured at the end of each 15 minute period before the next dose was given.

STAGE II

The optimal dose was then continued for 24 hours, with haemodynamic monitoring every three hours except when the patient was sleeping. After 24 hours the infusion was stopped and readings were taken every 30 minutes until they became stable. The infusion was then restarted at the previous dose for a further 24 hour period with measurements every three hours as before. At the end of the infusion readings were repeated every 30 minutes until they again became stable.

During the 48 hour period the rate of infusion was adjusted at the discretion of the clinician. If, however, patients needed additional treatment or had side effects they were withdrawn from the study.

ANALYSIS OF RESULTS

Results are given as mean (SE). We used analysis of variance by the least squares method to assess the significance of the treatment effect.[10]

Results

STAGE I

Table 1 shows the results of dose titration compared with the mean preinfusion values. One patient was excluded from this analysis because he did not receive 6 μg/kg/min of dopexamine, a satisfactory response having been obtained at the lower doses. At a dose of 6 μg/kg/min the cardiac index rose from 1·8 (0·2) to 2·8 (0·3) l/min/m^2, an increase of 57% ($p < 0·001$). This resulted from increases in heart rate from 97 (6) to 114 (5) beats/min (18%, $p < 0·001$) and stroke volume index from 19 (2) to 25 (2) ml/m^2 (32%, $p < 0·001$). Mean systemic and pulmonary artery pressures were unchanged. Systemic vascular resistance fell by 34% from 2363 (260) to 1549 (298) dyn.s.cm^{-5} ($p < 0·001$) and the pulmonary vascular resistance from 233 (39) to 159 (29) dyn.s.cm^{-5} (32%, $p < 0·001$). Pulmonary capillary wedge pressure (diastolic pulmonary artery pressure) did not alter.

STAGE II

All patients then entered the second stage. Four were started on 6 μg/kg/min, five on 4 μg/kg/min, and one on 2 μg/kg/min. In two patients the dose was subsequently altered because of deteriorating symptoms.

Only one of the 10 patients completed the study. Three were withdrawn because of worsening dyspnoea, two as a result of symptomatic hypotension,

Table 1 *Short term haemodynamic response (mean (1SE)) to four doses of dopexamine in nine patients*

		Dopexamine dose				
	*Control**	*1 μg/kg/min*	*2 μg/kg/min*	*4 μg/kg/min*	*6 μg/kg/min*	*p‡*
HR (beats/min)	97 (6)	104 (6)†	107 (5)	111 (5)	114 (5)	<0·001
CI (l/min/m²)	1·8 (0·2)	2·1 (0·2)†	2·3 (0·2)	2·6 (0·2)	2·8 (0·3)	<0·001
MAP (mm Hg)	82 (3)	84 (4)	85 (4)	82 (4)	80 (5)	NS
SVI (ml/beat/m²)	19 (2)	21 (2)	22 (2)	24 (3)†	25 (2)	<0·001
SVR (dyn.s.cm⁻⁵)	2363 (260)	2105 (282)†	2014 (325)	1706 (269)	1549 (298)	<0·001
PAM (mm Hg)	41 (3)	42 (3)	43 (3)	42 (3)	42 (3)	NS
PVR (dyn.s.cm⁻⁵)	233 (39)	204 (35)	206 (31)	186 (34)†	159 (29)	<0·001
PCWP/DPAP	31 (2)	33 (3)	32 (3)	31 (5)	31 (5)	NS

*Control values are the mean of two baseline readings.
†Lowest dopexamine dose that produces a significant treatment effect.
‡Statistical significance of treatment effect.
HR, heart rate; CI, cardiac index; MAP, mean arterial pressure; SVI, stroke volume index; SVR, systemic vascular resistance; PAM, pulmonary artery mean; PVR, pulmonary vascular resistance; PCWP, pulmonary capillary wedge pressure; DPAP, diastolic pulmonary artery pressure.

and one because of failure to respond during either stage. Two patients were withdrawn because of possible side effects and one asked for the study to be stopped because of increasing malaise in association with a falling cardiac index. Two patients were withdrawn from the study within the first six hours and the remainder between 15 and 24 hours.

Table 2 shows serial measurements of haemodynamic variables in the eight patients in whom the infusion continued for at least 15 hours. The mean preinfusion values are compared with those in stage I after three hours, and when they were repeated at 15–18 hours on the same dose of dopexamine.

On the dose selected, cardiac index initially rose by 56% and stroke volume index by 35%, and although the treatment effect was still significant after three hours, both variables had returned to the control values by 18 hours. A similar pattern was seen for systemic and pulmonary vascular resistance, which fell by 34% and 33% respectively. Again a significant reduction was still present after three hours but both returned to control values within 18 hours.

By 18 hours only heart rate remained significantly different from control values. Pulmonary capillary wedge pressure (diastolic pulmonary artery pressure), mean arterial pressure, and mean pulmonary artery pressure did not alter during the infusion.

Figure 1 shows the change in cardiac index during the infusion in all 10 patients. For reasons of clarity, we did not include two measurements that were taken after the dose of dopexamine was changed. During the period of infusion cardiac index declined in all 10 patients.

Figure 2 shows the results obtained in the only patient who completed the protocol. After an initial response the cardiac index fell with time to approach the preinfusion value after 24 hours. Restarting the infusion after one hour resulted in partial restoration of the initial treatment effect which again declined with time. When the infusion was abruptly stopped after each 24 hour period the cardiac index fell to below its preinfusion value.

UNWANTED EFFECTS

In one patient ventricular fibrillation developed after 21 hours on 6 μg/kg/min dopexamine. There had been no preceding history of arrhythmias and after resuscitation the serum potassium was 3·6 mmol/l. Ventricular fibrillation did not recur after the infusion was stopped and the pulmonary artery

Table 2 *Haemodynamic response in eight patients during dose titration (stage I) and continuous infusion compared with preinfusion values (mean (1 SE))*

	Control†	*Stage I*	*3 h*	*15–18 h*
HR (beats/min)	95 (6)	108 (6)***	105 (5)***	107 (5)***
CI (l/min/m²)	1·8 (0·2)	2·8 (0·3)***	2·6 (0·3)***	1·9 (0·2)
MAP (mm Hg)	83 (4)	80 (6)	82 (6)	79 (6)
SVI (ml/beat/m²)	20 (3)	27 (3)***	25 (3)***	19 (3)
SVR (dyn.s.cm⁻⁵)	2352 (277)	1556 (312)**	1826 (451)**	2254 (434)
PAM (mm Hg)	40 (3)	38 (4)	39 (3)	41 (1)
PVR (dyn.s.cm⁻⁵)	214 (48)	144 (35)*	155 (46)*	194 (34)
PCWP/DPAP (mm Hg)	31 (3)	28 (3)	29·5 (3)	31 (1)

*p < 0·05; **p < 0·01; ***p < 0·001.
†Mean of two baseline readings.
See table 1 for abbreviations.

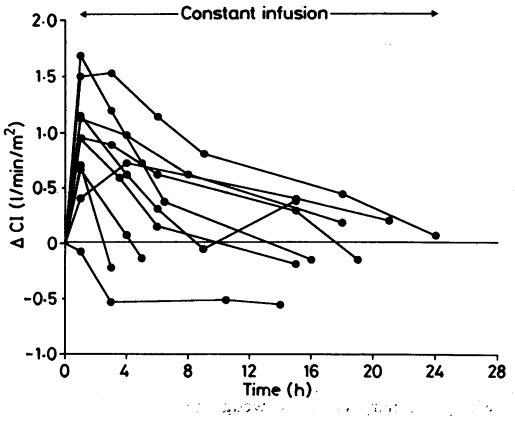

Fig 1 *Change in cardiac index (△ CI) in 10 patients during dose titration and constant infusion of dopexamine.*

catheter was removed. This patient was also taking flosequinan and an interaction between the two agents cannot be excluded. In the patient who completed the study ventricular tachycardia developed four hours after the infusion had been stopped. No important arrhythmias were seen in the other eight patients.

In the insulin dependent diabetic, glycaemic control became worse but ketosis did not develop. Over the preceding 48 hours his blood sugar had ranged from 6 to 13 mmol/l. After 15 hours on 4 μg/kg/min dopexamine his blood sugar had risen to 23 mmol/l and he experienced intense nausea. Over this period he had received 35 g of dextrose by infusion (for thermodilution and dopexamine administration) and he was also confined to bed. Both factors may have contributed to the development of hyperglycaemia, but β_2 adrenoceptor stimulation by dopexamine could also have been responsible. Glycaemic control was not assessed in the other diabetic patient because breathlessness led to the infusion being stopped after three hours.

In four of the 10 patients nausea developed during the infusion and caused vomiting in one patient. No other side effects were reported.

Discussion

This study confirms the impressive acute haemodynamic response to dopexamine that has previously been reported.[8 9] Short term infusion increased the cardiac index, heart rate, and stroke volume index; reduced systemic and pulmonary vascular resistance; and did not change mean arterial pressure. When Dawson *et al* used a similar dose range the mean rise in the cardiac index was 132%[8] compared with 57% in the present study. The difference in magnitude of response may reflect differing severities of heart failure in the two patient groups.[11] They also reported a slight fall in the left ventricular end diastolic pressure which was not seen in our patients.

During the second stage of our study there was a progressive decline in treatment effect with time. After 18 hours only heart rate remained significantly different from the control value. In the one patient who completed the study, the initial response was partly restored when the infusion was stopped for one hour but there was a further decline with time.

Haemodynamic deterioration resulted in withdrawal of six of the 10 patients, two further patients being withdrawn because of possible side effects. Nausea in four patients was probably caused by stimulation of dopamine receptors in the chemoreceptor trigger zone.[3]

The important feature of this study was the rapid decline in therapeutic effect with time. The clinical state of the patients was considered to be stable before they entered the study and cannot explain this finding. Downregulation of adrenoceptors follows prolonged exposure to agonists[12 13] but in patients with heart failure receiving dobutamine this is only apparent after 72 hours.[14 15]

It is unwise, however, to draw direct comparisons with previous studies and the findings of the present study should be interpreted with caution. The number of patients was small and all had severe chronic heart failure. If adrenocepter downregulation is indeed the mechanism responsible, premature downregulation may result from reduced adrenocepter number[16] and sensitivity,[17] which reflect the severity of myocardial dysfunction. Furthermore, the dopexamine dose, level of response obtained, and the concomitant use of oral vasodilators[18 19] may all affect the rate of downregulation. Differences in

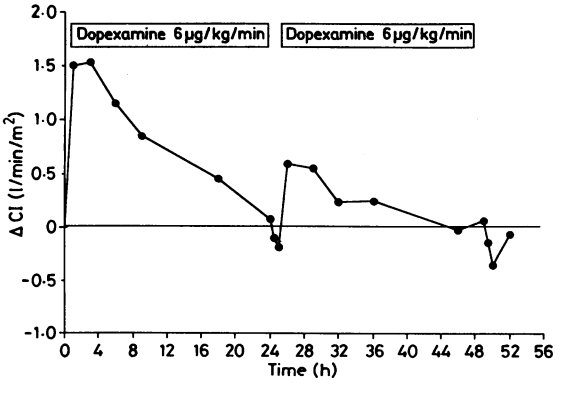

Fig 2 *Change in cardiac index (△ CI) during dopexamine infusion in the one patient who completed the study. The two 24 hour periods are separated by a break of one hour.*

patient selection may help to explain the apparently contradictory findings of Colardyn *et al*,[20] who did not find tolerance to dopexamine in a study similar to the present one.

Finally, although chronic heart failure is the model frequently chosen, agents such as dopexamine are used primarily in the setting of acute heart failure where the adrenocepters are likely to be normal.

Clearly further studies are required, both in acute and chronic heart failure, and these should include direct comparison with existing agents. Until, however, the question of tolerance has been resolved dopexamine cannot be recommended for the treatment of chronic heart failure.

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